Reviewer's report

Title: Use of Case Reports and the Adverse Events Reporting System in Systematic Reviews: Assessing the link between Crohn's Disease Medications and Hepatosplenic T-Cell Lymphoma

Version: 1 Date: 18 April 2013

Reviewer: Norman Marks

Reviewer's report:

Major Compulsory Revisions

1. I believe that within the substance of this submission, but not properly developed or discussed, is an important message for both clinicians and researchers who access this journal -- the pressing need, within systematic reviews, to consider methods to improve the process of data collection on drug adverse events that would increase the quality of the evidence of harms associated with a given pharmacological therapy – especially for rare, unexpected, and serious/fatal AE’s…… so that, with improved quality of evidence, the risk/harm side of a benefit-risk assessment can properly support a strong recommendation for treatment.

Without a major revision of the article’s discussion section to further identify, develop and suggest methods of case report data quality improvement -- the key message to the general reader, I cannot recommend publication of the article as written. The study’s stated result, “Consistent with FDA safety warnings, we confirmed that anti-metabolites, anti-TNFa’s, and cyclosporine have a possible causal association with HSTCL” is information already well recognized and previously published.

2. Although mentioned rather obliquely in their discussion section, the authors do arrive at this key (poor data quality in case reports) message by reporting almost incidentally as a secondary study finding that the poor quality of the data available to them in case study reports, from both the published literature and the FDA AERS reports …. the lack of standardization of data elements necessary for evaluating the association between the HSTCL adverse event and the drug therapies…… prevents adequate assessment of harm or risk. However, this key message is neither reflected in the title of the study or the abstract, nor have the authors developed this insight in the discussion or conclusion sections.

3. I do not believe that the study design/methods, a literature review with identification of 37 unique cases of HSTCL in patients with Crohn’s disease and application of causality assessment tools to those cases represents significant new information not already available in published literature to readers. As a stand alone result, without the further development of discussion/conclusions as described above, this case series would not merit approval for publication.
4. I do not believe that the authors use of the Naranjo causality scale and related instruments is generally recognized in 2013 as a preferred method for reaching more certainty about causality for this type of serious/fatal, but rare ADR. As noted in their Chou et al. reference (36), the basis for the AHRQ methodology guide, case reports are considered as hypothesis-generating, or perhaps hypothesis-strengthening, data sources, with more rigorous observational studies used to achieve more certainty of a causal relationship between drug and adverse outcome. For me, the results described – all three tools generating a “possible” causality score for all treatment drugs - would not merit approval for publication.

5. In an attached document, I have provided a few comments on my perspective on directions that these authors might develop in the discussion section …… suggestions for improvement in the quality of the data in case series sources that would support future systematic reviews.

Minor Essential Revisions

I would only suggest the minor factual correction in the Background section……..”a black box warning was issued in 2006 for the anti-TNFa’s and HSTCL”…………more accurately, I believe, a warning about the observed association between HSTCL and use of Remicade/infliximab was added to the Boxed Warning for Remicade in May 2006.

Discretionary Revisions - none

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Systematic Reviews currently considers the following article types: Commentary, Letter, Methodology, Protocol, Research and Systematic review update articles.

When assessing the work, please consider the following points:

1. Is the question posed by the authors new and well defined?
   Authors state: "We will also discuss the implications of our findings for the use of case reports in systematic reviews."….this should be focus of discussion and appears to be inadequate in current version.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
   Yes, the description of the literature review and AERS database access and the elimination of duplicates is well described. The application of the three ‘causal assessment’ tools is also well described.

3. Are the data sound and well controlled?
   Does not apply to this article.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Does not apply – or likely so.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

The discussion needs both tailoring and refinement and consideration of a focus on the need for future improvement in the process for capturing better primary data in individual case reports, methods for organizing the collection of primary data for secondary uses (such as research and public health reporting) by use of prospective registries, managed by either medical care organizations (e.g. K-P) or professional societies (e.g. Am Soc. Of Anesthesiologists) and the coordination of these private activities with the public health work of the FDA in drug/device post-market surveillance.

6. Do the title and abstract accurately convey what has been found?

I believe that the title and the abstract could be improved once the discussion section of the paper addressed the modifications in focus noted elsewhere in these review comments.

The title’s elements before the “:” might focus on the ‘use of case report data to inform systematic reviews’……and after the colon might address the need for higher quality case report data rather than the title’s current focus on their HSTCL data set, which I believe is not the “new” or most important content.

The same comments apply to the current abstract which, for me, are less interesting for their 37 HSTCL cases culled from the two sources and more interesting for their observations about the poor quality of the case report data and the inability of those case reports to support the systematic review…..and especially their recommendations for attention to increasing the acceptance of standards for case study data whether those standards are voluntary standards that originate from journal editors, from professional societies developing

7. Is the writing acceptable?

Yes, the writing is acceptable but I would suggest that the article can be considerably shorter, with a compact focus on the issue of the quality/lack of adequate data in the case reports and an expanded discussion about possibilities for improved case report data capture in order to permit future systematic reviews to use the case report data source as a more informed source for best practices information in CER, especially for the harms associated with interventions – the “risk” side of any risk=benefit analysis.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a
statistician.

Declaration of competing interests:

I have no financial or non-financial competing interests in relation to this paper.
Norman S. Marks MD, MHA